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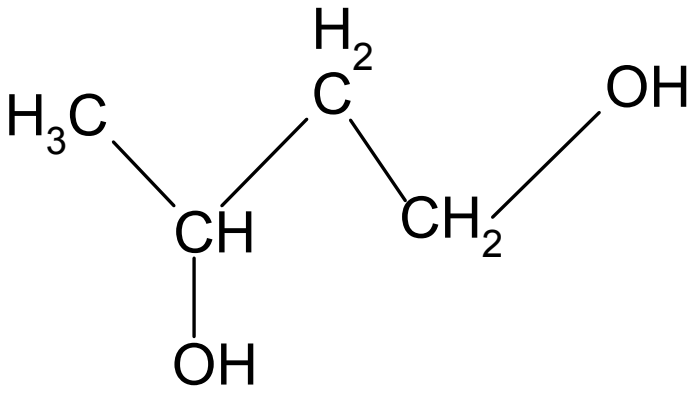
1,3-Butanediol

CAS Number 107-88-0



USEPA HPV Challenge Program Submission

Revised Test Plan

July 14, 2003

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Executive Overview

1,3-Butanediol is a diol used as a chemical intermediate in the manufacture of polyester plasticizers and other products. It finds some use as a solvent for flavorings and as a humectant in pet foods, tobacco and cosmetics. The U.S. FDA sanctions the use of 1,3-Butanediol as a food additive in several direct and indirect applications. Use in cosmetics has been reviewed by the Cosmetic Ingredient Review, who published a report in 1985 concluding that 1,3-Butanediol was safe as presently used in cosmetics. Industrial exposures by the inhalation and dermal routes are considered minimal as the industrial uses are thought to be almost exclusively closed systems and the material has a relatively low vapor pressure.

Physicochemical properties of 1,3-Butanediol are well established and indicate that it is a slightly-volatile liquid with high water solubility. The value of the octanol-water partition coefficient suggests that 1,3-Butanediol will partition preferentially into water and has little potential for bioaccumulation.

The estimated half-life of 1,3-Butanediol vapor in air, due to indirect photolysis, is approximately 9 hours. The material is considered stable to hydrolysis in water. It was found to be readily biodegradable by the OECD criteria. Fugacity calculations indicate preferential distribution to water and soil. Toxicity to aquatic species was determined using direct investigation, SAR modeling and through the use of 1,4-Butanediol as a surrogate. The results indicate a low hazard potential for fish, aquatic invertebrates and aquatic plants.

Studies of 1,3-Butanediol metabolism show that it is readily converted by mammals to β-hydroxybutyraldehyde, which is in turn, rapidly oxidized to β-hydroxybutyrate. Subsequent metabolic steps lead to acetoacetate and acetyl CoA, followed by entry of acetyl CoA into the tricarboxylic acid cycle to produce carbon dioxide and reducing equivalents that are converted to ATP by the electron transport chain. In addition, acetyl CoA is a central intermediate metabolite in lipid biosynthesis and can be converted to sterols and fatty acids.

Acute toxicity is minimal by the oral and inhalation routes, and repeated-dose administration of high doses to experimental animals and humans does not produce adverse effects until the amount ingested becomes a significant contributor to the individual's caloric requirement. Even then, the observed effects are limited to minor reduction in body weight gains and alterations in serum glucose, ketone bodies and fatty acid synthesis resulting from the metabolism of 1,3-Butanediol as a nutrient. Multigenerational and developmental toxicity studies produced no remarkable findings. Genotoxicity studies indicate lack of genototoxic effects and chronic studies did not show any carcinogenic activity.

No additional toxicity testing is recommended for this well-studied and essentially non-toxic material.

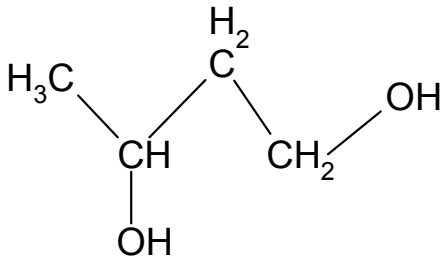
Testing Plan and Rationale

Testing Plan in Tabular Format

CAS Number 107-88-0 1,3-Butanediol	Information Available?	OECD Study ?	GLP Study?	Other Information ?	Estimation Method?	Acceptable?	Testing Recommended?	
HPV Endpoint								
Physical Chemical								
Melting Point	Y	N	N	Y	N	Y	N	
Boiling Point	Y	N	N	Y	N	Y	N	
Vapor Pressure	Y	N	N	Y	N	Y	N	
Partition Coefficient	Y	N	N	N	Y	Y	N	
Water Solubility	Y	N	N	N	N	Y	N	
Environmental & Fate								
Photo-Degradation	Y	N	N	N	Y	Y	N	
Water Stability	Y	N	N	Y	Y	Y	N	
Transport	Y	N	N	N	Y	Y	N	
Biodegradation	Y	Y	Y	Y	N	Y	N	
Ecotoxicity								
96-Hour Fish	Y	N	N	N	Y	Y	N	
48-Hour Invertebrate	Y	N	N	N	Y	Y	N	
72-Hour Algae	Y	Y	Y	N	N	Y	N	
Toxicity								
Acute	Y	N	N	Y	N	Y	N	
Repeated Dose	Y	N	N	Y	N	Y	N	
Genetic Toxicology *in vitro*	Y	N	N	Y	N	Y	N	
Genetic Toxicology *in vivo*	Y	N	N	Y	N	Y	N	
Reproductive	Y	N	N	Y	N	Y	N	
Developmental	Y	N	N	Y	N	Y	N	

Introduction

1,3-Butanediol, CAS Number 107-88-0 is a four carbon glycol with a sweet flavor and a bitter aftertaste (1). It is a clear, viscous, low-volatility liquid that is miscible with water and most polar organic solvents but only slightly soluble in ether. It is insoluble in aliphatic hydrocarbons, benzene, and carbon tetrachloride. Its most extensive use is as an intermediate in the manufacture of polyester plasticizers and other chemical products. It finds some use as a solvent and humectant; the structure is shown below:



1,3-Butanediol is also known as:

- 1,3-Butylene Glycol
- Beta-Butylene Glycol
- Butane-1,3-Diol
- 1,3-Dihydroxybutane
- 1-Methyl-1,3-Propanediol
- Methyltrimethylene Glycol

The chemical and physical properties of 1,3-Butanediol make it a unique solvent for certain applications and a useful chemical intermediate. The most extensive use for 1,3-Butanediol is as an intermediate in manufacture of certain polyester plasticizers (2). These plasticizers are valuable because of their compatibility with a broad range of polymers and the resultant stability of the plasticized material. This use currently accounts for about half the 1,3-Butanediol production.

Another important application is in the manufacture of structural materials for boats, custom moldings, and sheets and boards for construction applications. 1,3-Butanediol imparts resistance to weathering plus flexibility and impact resistance. It is also used in the manufacture of saturated polyesters for polyurethane coatings, where the glycol imparts greater flexibility to the polyester molecule. This application currently accounts for about 30% of the 1,3-Butanediol produced and includes coatings, foams and elastomer production. About one third of this (10% of the total production) goes into multifunctional monomer production for radiation-cured coatings.

1,3-Butanediol is an outstanding humectant (3), especially when compared with other glycol series humectants. It has the capability to acquire and maintain atmospheric moisture at nearly constant levels in the important 20-25% humidity range (4). 1,3-Butanediol is a highly effective humectant in pet foods, tobacco and cosmetic formulations. In cosmetic formulations it inhibits the drying out of cosmetics and the crystallization of insoluble components in cosmetic vehicles. Products employing this chemical are more resistant to high humidity. It is used as a humectant in cosmetics, especially in hair sprays and setting lotions (5). Currently about 10% of total U.S. 1,3-Butanediol production goes into personal-care products.

Miscellaneous end-use areas for 1,3-Butylene Glycol are in surfactants, inks, solvents for natural and synthetic flavorings and coupling agents in cellophane (4). These miscellaneous uses altogether account for a few percent of the 1,3-Butanediol usages in the United States.

Exposure in industrial applications is limited by process controls and protective equipment; however, there is no occupational exposure level set by any governmental agency. Manufacture of this material is in a closed system and the only significant exposure is in the open-cap loading of rail cars and tank cars. Workers doing the loading wear appropriate personal protective equipment and stay in the area where vapors are released only a short time. Use as a humectant in consumer products results in a low-level of inhalation exposure limited by the low volatility of this material. In some cosmetic applications, such as eye shadow or makeup foundations, use will result in dermal exposure. Extensive animal studies have shown that it is of low toxicity and actually serves as a mammalian nutrient.

Several fate and toxicity studies have been conducted on 1,3-Butanediol. These studies are briefly reviewed in this testing rationale document, which describes how they meet the SIDS (Screening Information Data Set) endpoints of the United States Environmental Protection Agency (USEPA) High Production Volume Challenge (HPV) program. Robust summaries have been prepared for key studies; supporting studies are referenced in these summaries or given as shorter summaries using the IUCLID format. The available data set satisfactorily fulfills the data requirements for the EPA HPV Program. Although all endpoints are not filled by experimental data, the estimation of some endpoints from SAR relationships is satisfactory for this low-hazard member of the aliphatic polyol family and encouraged to avoid unnecessary animal usage.

Approved Food Applications

The U.S.FDA and the Joint FAO/WHO Expert Committee on Food Additives have both evaluated 1,3-Butanediol for human dietary intake. JECFA has set an “Estimate of acceptable daily intake for man” of 0 to 4 mg/kg-body weight.

The FDA covers 1,3-Butanediol in several sections of the Code of Federal Regulations sanctioning both direct and indirect food additive applications.

FDA Sanctioned Food Application of 1,3-Butanediol		
21CFR Section	**Type Additive**	**Application**
172.712	Direct	In sausage casings as formulation aid or processing aid
173.220	Direct	Solvent for flavorings
175.105	Indirect	Component of food-contact adhesives
175.320	Indirect	Component of coating for food-contact polyolefin films.
177.1200	Indirect	Component of cellophane used in food-contact
177.1210	Indirect	Component of sealing gaskets for food-contact
177.1680	Indirect	Monomer for food-contact polyurethanes
177.2420	Indirect	Monomer for food-contact polyesters
178.2010	Indirect	Antioxidant and/or stabilizer for food-contact polymers

Cosmetic Applications

1,3-Butanediol is currently used in many personal care products. Its safety for these applications was reviewed by the Cosmetic Ingredient Review of the Cosmetic, Toiletry and Fragrance Association, which published a report in 1985 (6) concluding that 1,3-Butanediol was safe as presently used in cosmetics.

Physical-chemical Data

Physical-chemical data for 1,3-Butanediol are available from the literature and manufacturer's information.

Melting Point	-77˚ C (7)
Boiling Point	207.5 deg C @ 1013 hPa (7)
Vapor Pressure	0.027 hPa @ 25˚ C (8) 0.08 hPa @ 20˚ C (9)
Partition Coefficient	Log $K_{o/w}$ = -0.29 (10)
Water Solubility	Soluble in all proportions (3)

These properties indicate that 1,3-Butanediol is a slightly volatile liquid with high water solubility. The value of the partition coefficient suggests that 1,3-Butanediol will partition preferentially into water and has little potential for bioaccumulation.

Recommendation: No additional studies are recommended. The available data fill the HPV required endpoints.

Environmental Fate and Pathways

Biodegradation potential was recently determined using a modified Sturm Test according to OECD Guideline 301B. In this carbon dioxide evolution test, approximately 80% of the theoretical carbon dioxide production was achieved in 28 days using non-adapted domestic sludge (11). Thus, 1,3-Butanediol is considered readily biodegradable by the OECD criteria.

Photodegradation was estimated using version 1.90 of the Atmospheric Oxidation Program for Microsoft Windows (AOPWIN) that estimates the rate constant for the atmospheric, gas-phase reaction between photochemically produced hydroxyl radicals and organic chemicals. The estimated rate constant is used to calculate atmospheric half-lives for organic compounds based upon average atmospheric concentrations of hydroxyl radical. The program produced a estimated rate constant of 14.2329 E-12 cm3/molecule-sec. Using the default atmospheric hydroxyl radical concentration in APOWIN and the estimated rate constant for reaction of 1,3-Butanediol with hydroxyl radical, the estimated half-life of 1,3-Butanediol vapor in air is approximately 9 hours (see accompanying robust summary). No direct photodegradation is anticipated in the troposphere as this material is not expected to absorb light at > 290 nm.

Water stability has not been quantitatively determined for 1,3-Butanediol. Quantitative stability determinations are considered unnecessary for compounds containing only non-hydrolysable groups, as the SIDS manual states that consideration should be given to using an estimation method. There is no evidence available that 1,3-Butanediol is unstable in water and as it has no hydrolysable groups, the half-life in water is estimated with high confidence at greater than one year (12).

Theoretical Distribution (Fugacity) of 1,3-Butanediol in the environment was estimated using the MacKay model with standard defaults in EPIWIN v 3.05 but using the more conservative vapor pressure of 0.06 mm Hg (13). The results for distribution using a model calculated Ko/c (adsorption coefficient based on organic carbon content) of 0.21 are:

- Air 2.96 %
- Water 49.7 %
- Soil 47.3 %
- Sediment 0.074 %

Recommendation: No additional studies are recommended. The available data fill the HPV required endpoints.

Ecotoxicity

A recent GLP guideline (OECD 201) study of algal inhibition using measured concentrations of 1,3-Butanediol is available demonstrating low hazard to green algae after 72 hours of exposure (14). No studies of fish or invertebrate aquatic toxicology were found. ECOSAR estimates, using the neutral organic model are given in the table below. The justification for using ECOSAR estimates rather than actually testing this material is that tis class of materials (diols) is well characterized for aquatic toxicity and simple alcohols including diols (methanol, ethanol, 2-propanol, 2-methyl-2,4-pentandiol and 2-ethoxyethanol for fish; and ethanol, ethylene glycol and 2-ethoxyethanol for daphnia) were actually used to derive the SAR relationship for the neutral organics class (15). In addition, the concentrations that would have to be used to produce toxicity are far above the required maximum values that are generally tested and no useful information would be obtained from testing.

Aquatic Toxicity 1,3-Butanediol	
Fish, 96 hour LC_{50}	9494 mg/L*
Daphnia, 48 hour EC_{50}	8684 mg/L*
Algae, 72 hour EC_{50}	> 1070 mg/L (14)

* Estimated using ECOSAR (16)

These estimates are supported by the very high fish and daphnia EC50 values for the similar compounds 1,2-propanediol (17), 1,4-butanediol (18), 1,2-butanediol (19) and 1,2-ethanediol (20) that have been experimentally determined to be in the same range as that predicted for 1,3-Butanediol using the ECOSAR modeling program and SAR relationship contained therein. The SAR "neutral organics" relationship is verified to be a reasonably accurate predictor of actual toxicity by the predictions verses measured values for these surrogate compounds as shown below. Although the measured daphnia value for 1,4-butanediol is lower that the predicted value by almost an order of magnitude, the measured toxicity of 1,4-butanediol to daphnids is still in a range not to be of environmental concern.

Compound	Fish LC_{50} (mg/L)		Daphnids EC_{50} (mg/L)	
	ECOSAR	Measured	ECOSAR	Measured
1,4-Butanediol	8,100	>10,000	7,500	813
1,2-Butanediol	9,500	>1000	8,700	>1000
1,2-Propanediol	23,150	23,000	20,470	34,400
1,2-Ethanediol	47,000	27,540-49,300	40,260	46,300

Recommendation: No additional studies are recommended. The available data fill the HPV required endpoints without unnecessary aquatic animal usage. Although definitive experimental data are not available for fish and daphnia toxicity, the ECOSAR model predicts low hazard. The algae data prediction partially validates the ECOSAR modeling for this material and the low hazard of most other simple glycols also substantiates the estimates. As the estimates indicate EC50 values several fold greater than the usual limits of concentration in the standard OECD protocols (100-1000 mg/L), there is a high degree of confidence in the estimation of the acute EC50 values for fish and daphnids at > 1000 mg/L.

Health Effects

Several studies have been conducted to determine the potential health effects of 1,3-Butanediol. Generally speaking, results of these investigations have shown very little potential for adverse health effects from administration of even large quantities of 1,3-Butanediol to experimental animals or humans. A principle of toxicology is that if the body can handle a non-pharmacologically active compound using normal metabolic and excretion mechanisms then few compound-related adverse effects will occur. This principle is superbly illustrated in the case of 1,3-Butanediol, which can actually be used as a nutritional caloric source by mammals.

During an examination of the of the metabolism of various polyhydroxy compounds in rabbits, Gessner et al. (21) were unable to recover any recognizable metabolites of 1,3-Butanediol from the urine of treated animals. They postulated the 1,3-Butanediol was completely oxidized in the body by way of β-hydroxybutyrate. Kersters and DeLey (22) found that some species of bacteria oxidize 1,3-Butanediol using a soluble dehydrogenase. Tate et al (23) investigated the metabolic fate of 1,3-Butanediol in the rat and concluded that alcohol dehydrogenase (EC 1.1.1.1) catalyses the initial step in metabolism of 1,3-Butanediol to β-hydroxybutyraldehyde which is rapidly oxidized to β-hydroxybutyrate by aldehyde dehydrogenase. Subsequent metabolic steps to acetoacetate and acetyl CoA followed by entry of acetyl CoA into the tricarboxylic-acid cycle to produce carbon dioxide and reducing equivalents (that are converted to ATP by the electron transport chain) are well known biochemical pathways in mammals (24). Acetyl CoA is a central intermediate metabolite that can also be converted to sterols and fatty acids.

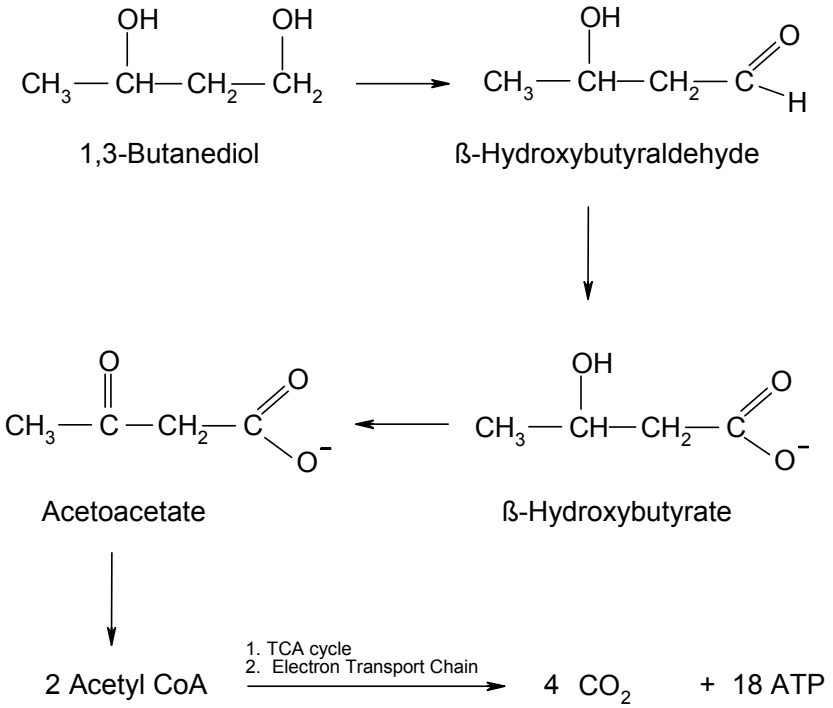


Figure 1: The mammalian metabolism of 1,3-Butanediol

From the established metabolic pathways it can be seen that 1,3-Butanediol is actually a reasonably good mammalian nutritional energy source. It has, in fact, been investigated as a "synthetic" food in cows, goats and humans with no adverse effects being reported. Discussion of the subject formed a symposium titled "Synthetic Food Additives as a Source of Calories: 1,3-Butanediol" at the 58th Annual Meeting of the Federation of American Societies for Experimental Biology in 1974.

Antidote for Ethylene Glycol Poisoning

In a 1992 report (25), the application of 1,3-Butanediol as an antidote for ethylene glycol intoxication was investigated by comparing it with ethanol, which is the standard therapy for ethylene glycol intoxication. The principle involved in the treatment is to inhibit the conversion of ethylene glycol to glyoxal, a process catalyzed by alcohol dehydrogenase (ADH). Studies had indicated that 1,3-butylene glycol (BG) binds to ADH more efficiently than EG and is less toxic orally than ethylene glycol or ethanol. In this study, male rats were divided into 5 groups of 6 animals each. Groups received by oral gavage either a single dose of ethylene glycol (32 mmole/kg), 1,3-Butanediol (39 mmole/kg, 3500 mg/kg) initially and every 6 hours up to 72 hours, ethanol (39 mmole/kg) initially and every 6 hours up to 72 hours, or ethylene glycol initially and then either 1,3-Butanediol or ethanol every 6 h up to 72 h. Administration of ethanol produced hepatotoxicity and pulmonary pathology as indicated by changes in clinical chemistry, urinalysis, and histopathology, while administration of 1,3-Butanediol alone did not. Neither ethanol nor 1,3-Butanediol produced any apparent nephrotoxicity. Ethanol produced ataxia, lethargy and central nervous system depression while 1,3-Butanediol did not. 1,3-Butanediol produced a higher concentration of urinary ethylene glycol indicating a better inhibition of ethylene glycol metabolism by ADH. Ethanol produced a higher EG blood concentration than BG. The higher EG blood concentration after ethanol administration may be partially attributed to dehydration and a decreased urine output as well as inhibition of ADH metabolism. Ethanol produced mortality in all animals prior to 72 hours. The ethylene glycol /ethanol combination produced mortality more quickly due to additive toxicity of the combination. Lack of any significant toxicity produced by 1,3-Butanediol and the production of significant toxicities by ethanol indicates that 1,3-Butanediol is potentially a better antidote than ethanol. Although this study was a not standard evaluation of toxicity, it serves to demonstrate the low toxicity of 1,3-Butanediol, which was administered at a dose of 3500 mg/kg every 6 hours for a period of 72 hours without producing significant toxicity. Furthermore, it confirms earlier observations that ADH is the initial enzyme involved in the metabolism of 1,3-Butanediol.

Acute Toxicity

Oral Exposure

Multiple determinations of the oral LD_{50} of 1,3-Butanediol were located in the open literature. These are elaborated in the table giving the LD_{50} value and the year of publication. One (Smyth et al. 1951) is written from the original literature as a robust summary giving what details were available in that publication. Although these older literature studies lack extensive experimental details, they generally have good reliability regarding the major findings. In this case, there are a total of three rats studies, a mouse study and a guinea pig study all providing similar results. The existing older studies, the known low repeated dose toxicity, the established metabolic route and the structural similarity to other low toxicity materials combine to provide high confidence that the rat oral LD_{50} is far in excess of the maximum dose of 2000 mg/kg, recommended as the limit of a modern acute toxicity test.

Acute Oral Toxicity Studies			
Author	**Species**	**LD_{50} (mg/kg)**	**Year of pub (ref)**
Symth H.F. Jr. et al.	Rat	22800	1951 (26)
Symth H.F. Jr. et al.	Rat	18610	1941 (27)
Loeser, A	Rat	18610-30000*	1949 (28)
Wenzel & Koff	Mouse	12980	1956 (29)
Symth H.F. Jr. et al.	Guinea pig	11500	1941 (27)

* Also includes two Symth studies in range of values

Inhalation Exposure

It has been reported that there were no deaths when rats were exposed to saturated vapor of 1,3-Butanediol for 8 hours (26). The actual concentration was not measured but based on the vapor pressure of 0.08 hPa the vapor concentration is calculated to be in the range of 80 ppm.

Dermal Exposure

No studies of the acute dermal toxicity of 1,3-Butanediol were found. Studies on the irritation of this material show that small quantities do not result in mortality (30).

Recommendation: No additional studies are recommended. The available data fill the HPV required endpoints for acute toxicity. Although the available studies do not meet the requirements of the current OECD guidelines,

the weight of evidence shows that the oral toxicity is very low. The conduct of additional studies would not add significantly to our understanding of this material's toxicity.

Repeat Dose Toxicity

Oral Exposure

Repeated-dose studies are available for two species. In a two-year feeding study in rats at 0, 1, 3 or 10% in feed, animals did not show any adverse effects related to treatment. The study used 30 rats of each sex per dose group and 60 rats of each sex in the controls. There was an interim sacrifice after 52 weeks of administration. Mortality, body weight gain, blood parameters, urine parameters, organ weights, incidence of neoplasm, and organ histopathology were unaffected by the two-year treatment at levels up to 10% in feed (31).

A two-year study in beagle dogs using dosed feed at 0, 0.5, 1 or 3% 1,3-Butanediol is also reported in the literature. In this study, 4 dogs of each sex per group were exposed to test substance. There was an interim sacrifice after 52 weeks of administration. Mortality, body weight gain, blood parameters, urine parameters, organ weights, incidence of neoplasm, and organ histopathology were unaffected by the two-year treatment at levels up to 3% in feed (31).

Eight-weeks dietary exposure of rats to 0, 5, 10, 20, 30 or 40% 1,3-Butanediol in the diet did not produce any signs of toxicity in a study reported in 1954 by Schlüssel (32).

A subchronic dosed feed study in dogs at 0, 3000, 6000, 9000 or 12000 mg/kg-day was conducted using groups of four dogs of each sex per dose level (33). In this study, reduction in body weight gain was observed at 9,000 and 12,000 mg/kg-day and was accompanied by organ weight, blood biochemistry, hematology, and behavioral changes. The treatment-related hematological changes were restricted to increases in platelet counts in the top two doses and an increased level of methemoglobin at only the high dose level. Biochemistry changes consisted of an increase in SGPT at the two highest doses, increased SGOT in the top dose group at 6-weeks but not at 13 weeks, and a dose-related increase in free fatty acids that was statistically significant only at the high dose. Relative organ weights of liver, kidney, brain, adrenals and lung were increased and relative weights of thymus and spleen were decreased at the top dose. At 9,000 mg/kg-day liver and kidney weights were increased. There were no pathological findings correlating with this upon either gross or microscopic examination. The most striking behavioral effect was epileptic-like seizures starting in the third week of the study in a high-dose animal. After the initial seizure, the number of dogs with seizures and the frequency of seizures increased with time affecting both males and females of the two highest-dose groups. Idiopathic epilepsy is known to occur in the colony of dogs used in this study; however, the seizures were dose-related. The 6000-mg/kg level was a NOAEL. Although the seizures were apparently dose related, they might have been secondary to metabolic alterations (e.g. reduced blood glucose levels) affecting CNS function in this colony of dogs with a predisposition to idiopathic epilepsy.

Oral Exposure, Nutritional Studies

In the early 1950s, research was conducted in Germany on synthetic calorie sources. Based on these initial investigations several groups have conducted extensive experiments in development of new synthetic sources of dietary calories for animals and man. 1,3-Butanediol was selected as the most promising "high-energy metabolite" and has been the subject of intensive study. Among these, the following studies reveal toxicologically relevant information regarding repeated dose exposure.

Rosmos et al. (34) looked at the effects of 1,3-Butanediol on hepatic fatty acid synthesis and metabolite levels in the rat. Groups of 10 male Sprague-Dawley rats were fed a basal diet containing 66.1% glucose, sucrose or the isocaloric equivalent of 1,3-Butanediol at 18% or 36% of the carbohydrate energy (1,3-Butanediol has an energy value of 6.5 kcal/g) for 23 days. A separate group of rats was given an i.p. injection of 800 mg 1,3-Butanediol. In vitro studies, using liver slices, were also performed with 10 mM 1,3-Butanediol as substrate.

Biochemical analyses indicated the plasma levels of glucose and triglycerides were significantly ($p < 0.05$) decreased in rats fed 1,3-Butanediol. Acute administration of 1,3-Butanediol to rats, on the other hand, increased the plasma levels of glucose. Free fatty acid plasma levels were not affected by single-dose administration of 1,3-Butanediol. Hepatic free fatty acid synthesis, however, was significantly ($P < 0.05$) decreased. Chronic administration of 1,3-Butanediol increased the liver levels of ß-hydroxybutyrate and acetoacetate. In vitro studies showed that 1,3-Butanediol decreased the conversion of glucose to free fatty acids in the liver without affecting the conversion of acetate to free fatty acids. It was speculated that 1,3-Butanediol may inhibit conversion of glucose to acetyl CoA. *In vitro*, release of pyruvate from liver slices was diminished but lactate release was not. Fatty acid synthesis in adipose tissue was not altered by 1,3-Butanediol administration. Data showed that 1,3-Butanediol was metabolized to ß-hydroxybutyrate and acetoacetate by rat liver. The lactate/pyruvate ratio was significantly ($p < 0.05$) increased, indicating that a shift towards a more reduced redox state in the cytoplasm after exposure to 1,3-Butanediol.

In a study to determine if depression of central nervous system from chronic ingestion of an alcohol is related to changes in brain metabolites, Veech et al. (1974) fed three groups of 10 male CFN Wistar strain albino rats standard rat diet for two weeks at which time their body weight was 270 g. These animals were fasted for five days, and then were fed commercial liquid diet in which 47% of the total calories were substituted with appropriate amounts of glucose, ethanol, or 1,3-Butanediol for a period of 62 days. The caloric values of glucose, ethanol, and BD are 3.68, 6.93 and 6.0 kcal/g, respectively. After treatment, brains and blood were analyzed for various metabolites. Brain lactate was significantly ($p < 0.005$) decreased in 1,3-Butanediol fed rats, as compared to glucose-fed rats. Levels of malate, aspartate, dihydroxyacetone phosphate, glucose-6-phosphate, ammonium ion, or creatinine phosphate were not affected by 1,3-Butanediol treatment. Brain glucose, however, was decreased 8-fold in 1,3-Butanediol treated rats compared to glucose treatment. Citrate and glutamate levels were higher in 1,3-Butanediol-exposed rats. Feeding of 1,3-Butanediol decreased blood glucose from 4.95 to 2.91 µmol/ml and increased blood ketone bodies.

Rosmos et al. (35) fed groups of rats, pigs, and chicks high fat basal diet containing 1,3-Butanediol at 0 or 17-19% of the dietary carbohydrate energy. They reported that feeding of 1,3-Butanediol significantly decreased ($p < 0.05$) the synthesis of free fatty acids in the rat liver, but not in pig liver or chick liver. Free fatty acids synthesis in the adipose tissue was unchanged in all species tested. The blood level of ß-hydroxybutyrate, acetoacetate, plasma levels of glucose, and triglycerides were increased by 48%, 24%, 89%, and 65%, respectively, in the 1,3-Butanediol-fed rats, as compared to controls. The blood levels of ß-hydroxybutyrate and acetoacetate in pigs and chicks were elevated, while the plasma glucose levels remained unchanged. The fact that the weight gain in rats, pigs, and chicks was not affected by 1,3-Butanediol at up to 20% of their dietary carbohydrate energy requirement suggested that rats, pigs, and chicks were able to utilize 1,3-Butanediol without loss of body weight at these levels. Their data further confirmed that 1,3-Butanediol decreases hepatic fatty acid synthesis in the rat and that 1,3-Butanediol is metabolized to hydroxybutyrate and acetoacetate.

Tobin et al. (36) have shown in several studies using human volunteers that isocaloric substitution of 1,3-Butanediol for starch caused less negative nitrogen balance and lower levels of blood glucose. In the fasting state and after glucose loading, however, concentrations of serum insulin and growth hormone were significantly increased. In one study, 12 young men and women were allowed a diet that contained 15 g of 1,3-Butanediol. Blood from each individual was analyzed for urea, proteins, haematocrit, haemoglobin, white blood cells, differential count, glutamic-oxaloacetic transaminase, glutamic-pyruvic transaminase, glucose-hydroxybutyrate, acetoacetate, lactate, pyruvate, triglycerides, free fatty acids, cholesterol, sodium, potassium, chloride, zinc, magnesium, and calcium. The results showed that feeding humans 1,3-Butanediol caused a significant reduction of urinary excretion of nitrogen as compared to those fed diet containing starch only. 1,3-Butanediol did not affect fecal excretion of nitrogen. Blood glucose levels were significantly lower in 1,3-Butanediol fed subjects. Feeding of 1,3-Butanediol did not alter any other biochemical, clinical, or haematological parameters. In another study by these investigators reported in the same communication, a group of 27 women were fed a diet containing 40 g 1,3-Butanediol per day without causing significant adverse effects.

Glucose tolerance tests conducted in a separate group of 10 men and women fed 1,3-Butanediol equivalent to 10% of the total energy intake for five days, showed no differences in levels of blood glucose during both glucose loading and fasting states. This suggests that humans can utilize 1,3-Butanediol at up to 10% of their total caloric intake without any adverse effects, with the exception that it may produce a hypoglycemic effect in some individuals (36).

Recommendation: No additional studies are recommended. The available data fill the HPV required endpoints for repeated-dose toxicity. The nutritional studies supply evidence that 1,3-Butanediol is metabolized by animals and by man as a dietary source of energy.

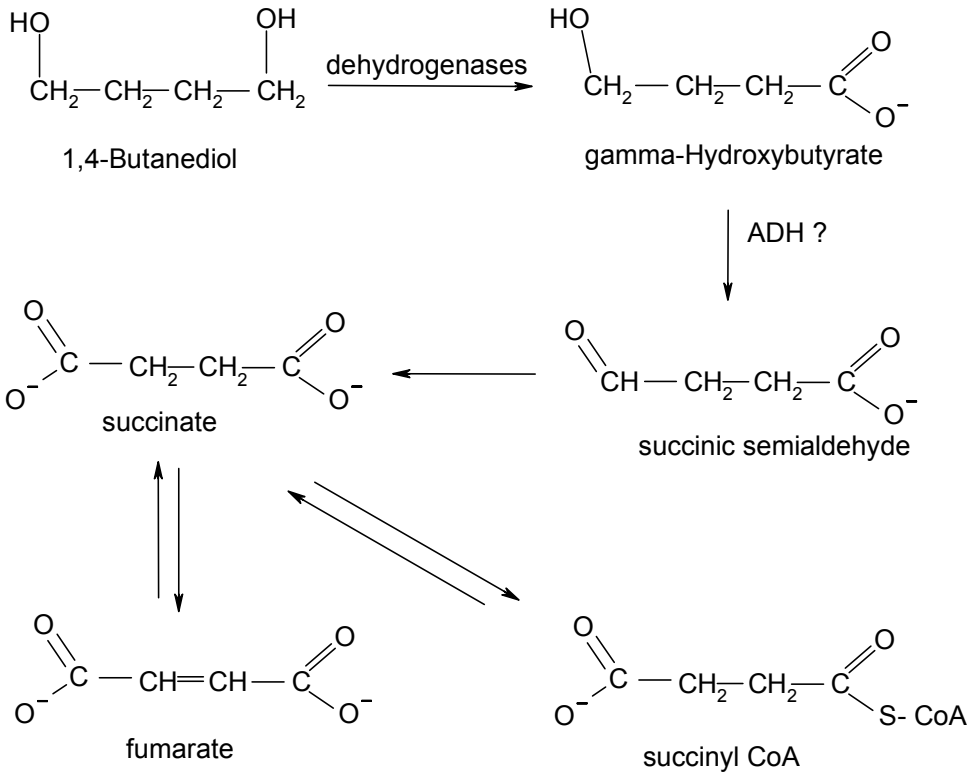
Genetic Toxicity

The SIDS/HPV requirement for genetic toxicity screening is for two end-points: generally one sensitive to point mutation and one sensitive to chromosomal aberrations. In the case of this material, adequate *in vivo* tests have been conducted that cover both of these two endpoints and, in addition, a 2-year study has indicated a lack of carcinogenic activity. Furthermore, this material is in a class of compounds without genotoxicity alerts.

Genetic Toxicology in vitro

In vitro tests of genetic toxicity for 1,3-Butanediol were not located. OECD 471 and 472 guideline studies were negative for the isomer, and close analog, 1,4-butanediol (see robust summaries, 37). Simple glycols, as a class, are not known to be genotoxic. There are two robust *in vivo* genotoxicity studies of this material. In addition, 1,3-Butanediol is rapidly metabolized in the body to β-hydroxybutyrate, which is a normal product of mammalian metabolism and not considered genotoxic.

Further justification for the use of 1,4-Butanediol as a surrogate comes from the metabolism of 1,4-Butanediol which indicates that like 1,3-Butanediol the ultimate fate of the carbons is carbon dioxide generated by the TCA cycle. The metabolic scheme with the most support for 1,4-Butanediol is shown below:



The pathway from γ-hydroxybutyrate to carbon dioxide is controversial (38) with early work suggesting that the tricarboxylic-acid cycle was primarily involved via succinate (39). Later investigators obtained substantial labeling of succinate and its amino acid metabolites in the brain of rats after intraventricular administration of [1-^{14}C]-labeled γ-Hydroxybutyrate (40). In addition, demonstration that the labeling pattern in the mouse brain after an intravenous injection of [1-^{14}C]-labeled γ-Hydroxybutyrate can be explained by oxidation via succinate, but not by ß-oxidation, eliminates beta-oxidation as a probable pathway (41). Data showing that γ-Hydroxybutyric acid is metabolized to γ-aminobutyric acid in incubated brain slices and that specific inhibitors of γ-aminobutyrate-2-oxoglutarate transaminase blocked the production of labeled γ-aminobutyric acid from labeled γ-Hydroxybutyric acid and of labeled 2-oxoglutarate from labeled glutamate, suggested that the catabolism of γ-Hydroxybutyric acid to γ-aminobutyric acid occurs via a transamination mechanism and not through the Krebs cycle (42). In spite of the transaminase pathway possibly having importance in the neurologic effects of γ-Hydroxybutyrate, the rapidity of 1,4-Butanediol's excretion and low degree of toxicity argue that a more generalized mechanism (such as intermediary metabolism and/or Krebs cycle) is prevalent. More recent work by Gibson and Nyhan (43) has shown that homogenates of liver and kidney mitochondria, but not heart, readily converted [U-^{14}C]-γ-Butyrolactone (the ring closed analog of γ-Hydroxybutyric acid) to ^{14}C organic acids via a pathway of conversion to ^{14}C-succinic acid, followed by further metabolism through the tricarboxylic acid cycle. Furthermore, this conversion was facilitated by exogenous NAD^+ and $NADP^+$. No evidence for the beta-oxidation of γ-Butyrolactone was obtained in any of the mitochondrial sonicates. Studies with exogenous non-labeled succinic semialdehyde indicated that this compound is an intermediate in the conversion of γ-Hydroxybutyric acid to succinic acid. Further evidence that succinate is involved in the metabolism of γ-Hydroxybutyric acid comes from the finding that patients with the rare genetic defect leading to succinic semialdehyde dehydrogenase deficiency (SSADH), accumulate γ-Hydroxybutyric acid in physiologic fluids (44). Based on these findings and considerations, the figure above presents the proposed primary initial metabolic pathways for 1,4-Butanediol. After conversion to succinate and fumarate, it enters intermediary metabolism where it is driven to carbon dioxide by dose-dependent mass balance. This rapid conversion into labile components of intermediary metabolism and the Krebs cycle is considered to account for its low systemic toxicity.

Although the pathways are different for 1,4-Buanediol and 1,3-Butanediol both funnel their carbons through the TCA cycle and looking at the intermediates one would predict that 1,4-Butanediol would be the more mutagenic of the two materials due to the succinic semialdehyde intermediate that is much more reactive with biological macromolecules than an α-ketoacid.

The other structural analog 1,2-Butanediol was also negative in the Salmonella reverse mutation assay in the chromosome aberration assay using CHL cells (45). A search of the literature did not reveal a definitive determination of the full metabolic pathway for 1,2-Butanediol. By analogy, the likely initial pathways involve common dehydrogenases that initially convert the diol to 2-hydroxybuteraldehyde then 2-hydroxybutyrate and finally to α-ketobutyrate. α-Ketobutyrate is known to be an intermediate in the catabolism of threonine and methionine and is metabolized to carbon dioxide and propionyl CoA (46). Propionyl CoA is converted to the four-carbon succinyl CoA by propionyl CoA carboxylase (47). Succinyl CoA is an intermediate in the TCA cycle and also a metabolic product of 1,4-Buteanediol.

Genetic Toxicology in vivo

Mammalian genotoxicity was assessed *in vivo* using both the dominant-lethal test in rats (males exposed for 13 weeks to 1,3-Butanediol at 0, 5, 10 or 24% by weight in the diet) and *in vivo* cytogenetics in rats, in which rat bone marrow cells were examined after multigenerational exposure from three different generations (F1A at 77 weeks post gestational exposure, F2A at 11 weeks post gestational exposure and F3A at 9 weeks post gestational exposure) exposed continually to test substance at 0, 5, 10 or 24% by weight in the diet, were examined for cytogenetic abnormalities (48). No effect on fecundity, fetal or gestational parameters were observed in the dominant lethal assay and the mutagenic index (resorptions as a percentage of implant sites) showed no trend with increasing dose of test substance in the diet. In the cytogenetic analysis, the frequency of occurrence of abnormal cells was found to be within the normal range for the F1A, F2A and F3A animals in this multigenerational study. No specific abnormalities were consistently observed in any dosed group and no dose-related effects were noted. Thus, neither of these studies produced results indicative of genotoxic activity of 1,3-Butanediol.

Recommendation: The SIDS requirement for genetic testing has been met as assays sensitive to both point mutation and to clastogenic effects have been conducted using an acceptable protocol. No additional testing is recommended.

Reproductive Toxicity

1,3-Butanediol has been subjected to a multigenerational study in which groups of 25 males and 25 female rats were mated for four successive generations with continuous exposure to 0, 5, 10, or 24% (approximately 0, 2500, 5000, or 12,000 mg/kg-day) test material in the diet. In one part of the study, F1 animals were mated for five cycles. In this part there, was a gradual decrease in the pregnancy rate at the high dose with no pups being produced after the fifth mating. Although the investigators suggested that this might be due to a decrease in male fertility associated with growth suppression, no substantiating evidence was obtained from histopathological examination of the gonadal tissues. For the other three generations of mothers (who generally underwent two mating cycles) and pups, all reproductive parameters were comparable among all groups.

Recommendation: No additional testing is required as the available data are sufficient to assess the reproductive toxicity of this material.

Developmental Toxicity

A developmental toxicity study was conducted as part of the multigeneration study of Hess et al. (see robust summary) (48). In this study, it was concluded that there were no definitive dose-related teratological findings in either soft or skeletal tissue. Fetotoxicity (e.g., delayed ossification of sternebrae) was noted at dietary levels of 10 and 24%. Because maternal toxicity parameters were not reported for the developmental toxicity portion of the study, examination of body-weight data reported for the other generations was used in the robust summary to assess maternal toxicity. The data suggests that the high dose levels do not significantly affect body-weigh gain in non-pregnant females; however, high-dose males gained less body weight. It is clear from other studies (cited in the robust summary for the Hess developmental toxicity study) that the dietary levels associated with fetotoxicity are also associated with significant metabolic disturbances due to the nutritional value of 1,3-Butanediol. Although the fetotoxicity was not clearly associated with maternal toxicity, what is clear is that these dose levels cause marked metabolic alterations, which could result in fetotoxicity. In conclusion, based on the metabolic disturbances, the exceedingly high dose level and the relative minimal fetotoxicity, 1,3-Butanediol is considered to have little or no activity as a developmental toxin.

Other investigators have shown metabolic disturbances in rats fed levels of 1,3-Butanediol in the range of the mid-dose level of this developmental toxicity study. For example, Rosmos et al. (35) reported that rats fed 17-19% of their carbohydrate requirement as 1,3-Butanediol had significantly decreased synthesis of free fatty acids in the liver and increased blood levels of beta-hydroxybutyrate (48%), acetoacetate (24%), plasma glucose (89%) and plasma triglycerides (65%). As these significant metabolic effects appear to occur at dose levels in the same range as the mid-dose of this developmental study and, as it is not known how this altered maternal metabolic profiles affects the conceptus, it is possible that the developmental delays (reduced ossification) are a direct result of the altered nutrient supply and not a direct effect of the test substance.

Another study was reported in 1986 by Mankes et al, (49) who dosed pregnant Long-Evans rats with 0, 706, 4206 or 7060 mg/kg-bw from 6 to 15 of gestation. These investigators reported that the high dose was associated with selective fetotoxicity of male pups not contiguous to a female pup. No malformations were reported at any dose level. As in the other developmental toxicity studies, this high-dose level is probably associated with significant metabolic alterations, yet only minor fetotoxicity was produced.

These studies are also supported by an investigation by Dysma (50), who reported that 1,3-Butanediol is without adverse reproductive or teratogenic effects in rats, dogs or rabbits.

Recommendation: No additional testing is required as the available data are sufficient to assess the developmental toxicity of this material.

Conclusions

With regard to the parameters specified in the EPA HPV Challenge program, the available information fills all of the requirements for physicochemical parameters, environmental fate, and toxicity information. No additional testing is recommended.

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